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Review article

Neural mechanisms of emotion regulation and their role in endocrine and immune functioning: A review with implications for treatment of affective disorders

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ABSTRACT

In the past century, medical progress has helped increase life expectancy and improve health outcomes more generally. Despite this progress, psychiatric disorders—especially affective disorders including depressive and anxiety disorders—are quite common and have been linked to dysfunction in endocrine and immune systems. In this review, we discuss neurobiological correlates of emotion regulation strategies and their effects on mental and physical health. Some of these correlates, namely sub-regions of prefrontal cortex, also play a key regulatory role in autonomic, endocrine, and immunological processes. Given this functional overlap, we propose a novel neuro-immuno-affective framework that targets improving emotion regulation, in order to: (1) *reduce* negative affect associated with depressive and/or anxiety disorders; and (2) *alter* endocrine and immune system functioning (e.g., reduce inflammation)—via changes in activity within (and connectivity between) brain systems that support (successful) emotion regulation. We conclude by arguing that such a framework can be adapted for psychiatric treatment protocols that holistically incorporate neural and immunological biomarkers to promote mental and physical health.

In the past century, advances in the medical sciences have helped extend life expectancy and health outcomes in the developed world. Despite this progress, there is consistently high prevalence of psychiatric disorders—especially in the affective domain. Currently, depression affects more than 322 million people worldwide—an 18.4% increase from 2005 (World Health Organization, 2017), and nearly 20% of adults (40 million) in the US alone are diagnosed with at least one anxiety disorder (National Institute of Mental Health., 2018; Ruscio et al., 2007). In addition to the negative toll depression and anxiety undoubtedly take on psychological health, there is mounting evidence that affective disorders often co-occur with dysfunction in immune and endocrine systems.

In general, psychological distress, especially when experienced early in life, is associated with chronically high (i.e., dysregulated) inflammation and other debilitating health conditions, including cardiovascular disease, some cancers, and type 2 diabetes (Fagundes et al., 2013a; Fagundes and Way, 2014; Miller et al., 2011). This same risk profile has also been observed in depressive and anxiety disorders. For example, individuals with a history of major depressive disorder (or who present with more depressive symptoms) tend to have exaggerated and/or prolonged inflammatory responses following acute challenges to the immune system, such as preventative vaccinations (Christian et al., 2010; Glaser et al., 2003), pregnancy (Maes et al., 2001), and even laboratory manipulations of social stress (Fagundes et al., 2013b; Pace et al., 2006; Weinstein et al., 2010). This growing evidence linking depression to altered immune system function has prompted many researchers doing translational work in health psychology and psychoneuroimmunology to develop models highlighting reciprocal, dynamic relationships between depression symptomatology and increased inflammation (Kiecolt-Glaser et al., 2015; Miller and Raison, 2016; Slavich and Irwin, 2014). In the case of anxiety disorders[1], a very similar picture seems to be emerging. In one study, individuals who fell within the clinical range for anxiety presented with higher levels of proinflammatory cytokine interleukin-6 (IL-6) than their non-anxious

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[1] Here, we think about and discuss depression and anxiety as they are defined by their respective symptomatology in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

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counterparts, even when controlling for age, sex, and depressive symptoms (O'Donovan et al., 2010). Other observational studies, with larger sample sizes (all Ns ≥ 400) and in independent cohorts, have provided converging evidence for the anxiety–inflammation link (Liukkonen et al., 2011; Pitsavos et al., 2006; Vogelzangs et al., 2013).

Given this immune dysregulation and increased risk for attendant health problems, it is vital to develop novel, theoretically-driven treatments for affective disorders that maximize efficacy and examine the role of these biobehavioral mechanisms. To date, clinicians have used pharmacological treatments and/or psychotherapy to treat anxiety and depression, but the efficacy rates of these approaches are not as high as many would want them to be. For example, in depression, the overall, meta-analytic effect size of antidepressant medications versus placebo is quite small (i.e., Cohen's $d < 0.2$; Fournier et al., 2010). A more recent and comprehensive meta-analysis of 21 antidepressants found slightly higher but still modest efficacy compared to placebo; odds ratios for individual drugs ranged from 1.37 (reboxetine.) to 2.13 (amitriptyline), or Cohen's $d = 0.17 - 0.42$ (Cipriani et al., 2018). Somewhat larger-sized effects are observed comparing combined, medication-*plus*-therapy treatment regimens (vs. medication alone), and even then effect sizes remain modest (i.e., Hedge's $g = 0.41$ for depressive disorders, 0.47 for anxiety disorders; Cuijpers et al., 2014). Extant psychotherapies intended to treat affective disorders are often amalgams of multiple regulatory strategies (e.g., Beck, 2011; Berking and Schwarz, 2014), so it is not immediately clear which elements of a given therapy make it more (or less) effective for which individuals, and for which situations in an individual's life—potentially confounding comparative studies of multiple therapies (e.g., Cuijpers et al., 2008). In contrast, a promising new avenue for treating depression incorporates immuno-based, pharmacological therapies (Raison et al., 2013; for a review, see Miller and Raison, 2016). We acknowledge this innovative line of work, but it will not be the focus of the present review. As will be discussed and argued for below, emerging evidence concerning neurobiological mechanisms supporting affective experience and regulation may provide another platform from which scientists and clinicians alike can develop comprehensive, targeted interventions to treat depression and anxiety.

With the development of non-invasive brain imaging, such as functional magnetic resonance imaging (fMRI), recent work in human neuroscience has revealed reliable brain mechanisms that support successful emotion regulation—an ability that is adaptive in general, but especially so for those individuals diagnosed with affective disorders. In this review, we highlight these findings, and also draw upon the growing literature on reciprocal relationships between central nervous system (CNS) activity and endocrine/immune system functioning. Indeed, some of the key brain regions involved in emotion regulation—namely, sub-regions of prefrontal cortex—have also been implicated in modulating activity in the endocrine and autonomic nervous systems—both of which are tightly coupled to (and influence) immune functioning.

Given this functional and anatomical overlap, we propose a novel, neurobiologically-grounded framework that focuses on improving people's use of adaptive emotion regulation strategies in order to *reduce* negative affect associated with depressive and/or anxiety disorders and concurrently (2) *alter* endocrine and immune system functioning (e.g., reduce inflammation). We hypothesize that these effects might be mediated via changes in activity within (and connectivity between) brain systems recruited by emotion regulation related processes. We conclude by arguing that this framework can be adapted for psychiatric treatment protocols that holistically incorporate neural and immunological biomarkers to promote mental and physical health.

1. Effects of emotion regulation strategies on mental and physical health

In the late 1990s, when there was renewed interest in psychophysiological processes related to the experience and regulation of emotion, James Gross proposed the well-known and influential process model of emotion regulation (Gross, 1998). In this model, there is a critical distinction between antecedent-focused regulatory strategies, which can be employed *before* or *while* an emotion is generated, and response-focused strategies, which involve modulating an emotional response *after* it has already been generated and experienced. Cognitive reappraisal, whereby someone changes the meaning of an emotionally evocative stimulus to alter its impact, is an example of an antecedent-focused strategy, whereas expressive suppression, which involves actively inhibiting outward expressions of one's inner emotional state (e.g., putting on a "poker face" while inwardly feeling some intense emotion) is a response-focused strategy.

Substantial and converging evidence across observational and intervention studies in healthy controls suggests that antecedent-focused strategies, especially cognitive reappraisal, are often more adaptive than response-focused strategies, such as expressive suppression.[2] Specifically, cognitive reappraisal has been associated with significant reductions in negative affect and physiological arousal, indexed by both psychological (e.g., subjectively experienced affect) and brain regions that process affect (i.e., the amygdala) (Denny et al., 2015a; Gross, 1998, 2014; McRae et al., 2010; Ochsner et al., 2004; Ray et al., 2010; Urry, 2010). On the other hand, response-focused strategies (i.e., expressive suppression) are relatively less adaptive, leading to dysregulated emotional responding and negatively impacting health (Appleton et al., 2014; Denson et al., 2011; Gross and John, 2003; Gross, 2014; John and Gross, 2004; Otto et al., 2018; Webb et al., 2012).

In clinical populations, depressed individuals are more likely to spontaneously and excessively use suppression, but can successfully implement cognitive reappraisal when instructed to do so (Ehring et al., 2010). This is consistent with studies that have shown that in other clinical populations, after receiving sufficient instruction and training, people can engage in cognitive reappraisal and other emotion regulation strategies (e.g., those with avoidant personality disorder; Denny et al., 2015a; those with social anxiety disorder, Goldin and Gross, 2010), although targeting and enhancing individuals' perceived self-efficacy (in engaging in cognitive reappraisal) may be needed in some cases to improve outcomes (e.g., for those with social anxiety disorder; Goldin et al., 2012).

2. Neural correlates of emotion regulation and autonomic and endocrine functioning

As fMRI and other brain imaging techniques have become more accessible in the past few decades, researchers in clinical and affective neuroscience have identified the neural bases of various psychological processes, including emotion regulation. Buhle et al. (2014) conducted a meta-analysis of main effects of cognitive reappraisal on brain activity across 48 neuroimaging studies (Buhle et al., 2014). The meta-analysis revealed that areas of prefrontal cortex, including dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC), were reliably activated during reappraisal of emotionally evocative stimuli (relative to a baseline condition, which simply measured participants' natural responses to the same kind of stimuli). Moreover, Buhle and co-authors found that reappraisal modulated (i.e.,

[2] This is a slight generalization, as the appropriateness of a given strategy is dependent on the situation and other factors (e.g., the initial intensity of the experienced emotion; it has been shown that cognitive reappraisal is difficult to employ with especially intense negative emotions). However, the cited research suggests that, in most situations with moderate arousal and negative valence, the net effect of cognitive reappraisal on health is positive, whereas the net effect of expressive suppression (especially if a person's preferred, most frequently employed strategy) is negative. However, with stimuli that induce very strong negative affect and/or high arousal, other strategies involving attentional deployment (e.g., distraction) may be preferable, at least initially.

diminished) activity exclusively in bilateral amygdala, a key sub-cortical region that processes valence of emotional stimuli. This is consistent with other studies that have more directly tested the role of PFC–amygdala relationships in predicting self-reported indices of successful cognitive reappraisal (Lee et al., 2012; e.g., Wager et al., 2008).

In addition to DL- and VLPFC regions implicated in reappraisal in Buhle et al.'s (2014) meta-analysis, Diekhof et al.'s (2011) meta-analysis identified another region of PFC, ventromedial PFC (VMPFC), in successful down-regulation (i.e., dampening) of affective responses to negatively-valenced stimuli, as measured by reduced amygdala activity (Diekhof et al., 2011). Importantly, VMPFC has neuroanatomical connections to both lateral PFC as well as the amygdala (e.g., Price, 2005). Taken together, these findings suggest that successful emotion regulation (e.g., via cognitive reappraisal) rests on the function of multiple PFC sub-regions (namely V/DLPFC and VMPFC) working in concert.

A different pattern emerges in the case of emotional suppression, as far as features of brain structure (physical properties) and function (activity to index psychological processes of interest). In one study, individuals who reported more frequently using emotional suppression as an emotion regulation strategy had lower VMPFC volume (Welborn et al., 2009). More recently, individual differences in suppression were associated with altered information processing efficiency in multiple brain networks, especially in the default mode network and frontoparietal control network, such that those with higher expressive suppression scores exhibited lower efficiency (Pan et al., 2018). Notably, VMPFC is a key hub in the default network, and multiple nodes of the frontoparietal control network are localized in V/DLPFC (Power et al., 2011).

Given this neurobiological groundwork, an important question is the extent to which these neural correlates of emotional reactivity and regulation are also involved in monitoring and/or modulating activity in other physiological systems. Indeed, this is critical for understanding the complex etiology and symptomatology of affective disorders, especially depression and anxiety, which are not only marked by recurring negative affect but also by dysregulation in the immune system, as described above. There has already been some work revealing links between (1) the central and peripheral (i.e., autonomic) nervous system (ANS); and (2) the CNS and endocrine system, specifically the hypothalamic–pituitary–adrenal (HPA) axis. Interestingly, across both of these research corpora, the VMPFC has consistently been identified as subserving important regulatory functions. First, with regard to CNS–ANS links, an initial neuroimaging study by Wong et al. (2007) established that VMPFC plays a modulatory role in parasympathetic activity, specifically controlling heart rate (Wong et al., 2007). More recently, Sakaki et al. (2016) demonstrated that higher resting state connectivity between VMPFC and the amygdala was associated with greater heart rate variability (HRV) (Sakaki et al., 2016)—a known peripheral biomarker of both pathophysiology and psychopathology, with specifically *low* HRV putting people at higher risk of emotion dysregulation (Thayer and Lane, 2009, 2000). This is consistent with other studies, including a meta-analysis by Thayer et al. (2012), that have provided confirmatory evidence that medial PFC plays an important role in modulating downstream cardiovascular functioning (Gianaros and Wager, 2015; Thayer et al., 2012; Wager et al., 2009a, b). As far as relationships between the CNS and the endocrine system, converging lines of research across animals (Diorio et al., 1993; Radley et al., 2006) and humans (e.g., Urry et al., 2006) have shown that prefrontal cortex, especially medial PFC, helps regulate the stress response along the HPA axis via connections to the amygdala and especially the hypothalamus.

Although the brain bases of emotion regulation and regulation of the ANS and endocrine systems have generally been examined in separate research programs, there seems to be growing evidence of shared neural correlates (especially medial portions of PFC) that are important for regulation of affect as well as downstream ANS/endocrine functioning.

3. Neuro-immuno-affective framework

In both animal and human models, research in psychoneuroimmunology has revealed interactions between the central nervous system (CNS), HPA axis, and immune system functioning via multiple pathways (Ader et al., 1990; Dantzer and Wollman, 2003; Dantzer, 2017; Marques-Deak et al., 2005). First, activity in the ANS, originating in various nuclei in the brain stem, modulate inflammatory responses in the periphery. This is achieved via a pro-inflammatory pathway consisting of sympathetic innervation—via norepinephrine signaling—of multiple immune cells, including macrophages, CD4 + T cells, CD8 + T cells, and NK cells (cf. Fagundes et al., 2017). This results in increased expression of protein complex *nuclear factor kappaB* (NF-κB), which in turn increases production of pro-inflammatory cytokines. There are also reciprocal interactions with the endocrine system in this pathway that promote inflammation, with increased cytokine production (from NF-κB expression) impairing functioning of glucocorticoid receptors and preventing cortisol from exerting its (normal) anti-inflammatory and immunosuppressive effects; this then further potentiates the inflammatory response due to un-regulated cytokine expression (cf. Kiecolt-Glaser et al., 2015). Moreover, in the case of chronic stress marked by high levels of circulating cortisol, immune cells become desensitized to anti-inflammatory effects of glucocorticoids and this leads to un-checked expression of cytokines and an enhanced inflammatory response (Fagundes and Way, 2014).

In the other, cholinergic anti-inflammatory pathway, parasympathetic activity along the vagus nerve—via release of acetylcholine—counteracts sympathetic activity and produces anti-inflammatory effects, as indexed by reduced expression of cytokines (Pavlov et al., 2003). Another body of work in social neuroscience has provided initial evidence for a link between CNS activity (i.e., activity in amygdala and other regions that support threat-detection and modulate stress responses) and acute changes in peripheral inflammatory responses (Muscatell and Eisenberger, 2012; Muscatell et al., 2015).

Given these known pathways between the CNS and immune system, as well as abovementioned evidence for neural correlates related to regulation of emotion and modulation of ANS/endocrine systems, we propose a novel, "neuro-immuno-affective" framework that incorporates emotion regulation skills training *and* brain and immunological biomarkers that reliably index mental and physical health. Specifically, the goal of this framework is to improve emotion regulation skills—especially among those diagnosed with depression and/or anxiety disorders—in order to *reduce* negative affect and *alter* immune system functioning (e.g., reduce an unchecked, proinflammatory response) (see Fig. 1 for overall schematic depiction of the framework).

We submit that these changes in immune system can be accomplished via changes in brain systems that support successful emotion regulation (e.g., V/DLPFC) and/or in regions that perform "double duty" by helping to regulate emotional responses *and* modulate ANS/endocrine systems (i.e., VMPFC; see Fig. 1A for PFC targets labeled on lateral and medial surfaces of a normalized (template) brain). Indeed, initial studies that have involved training emotion regulation skills (i.e., reappraisal) in healthy individuals have shown evidence of longitudinal, training-induced changes in self-reported affect (Denny and Ochsner, 2014), as well as in the neural correlates of successful emotion regulation, with attenuation of amygdala activity following reappraisal training (Denny et al., 2015b). Additionally, Creswell et al. (2016) found that a relatively brief (3-day) training in mindfulness mediation—a practice shown to regulate emotions (e.g., Goldin and Gross, 2010)—altered patterns of brain connectivity (including a region of DLPFC) and mitigated inflammatory responses (as measured by circulating IL-6 levels) four months post-training (Creswell et al., 2016). Another study implementing real-time fMRI feedback training found reliable increases in connectivity between areas of VMPFC/rostral anterior cingulate cortex and the amygdala during up-regulation of (positive) emotions over the course of one relatively brief laboratory

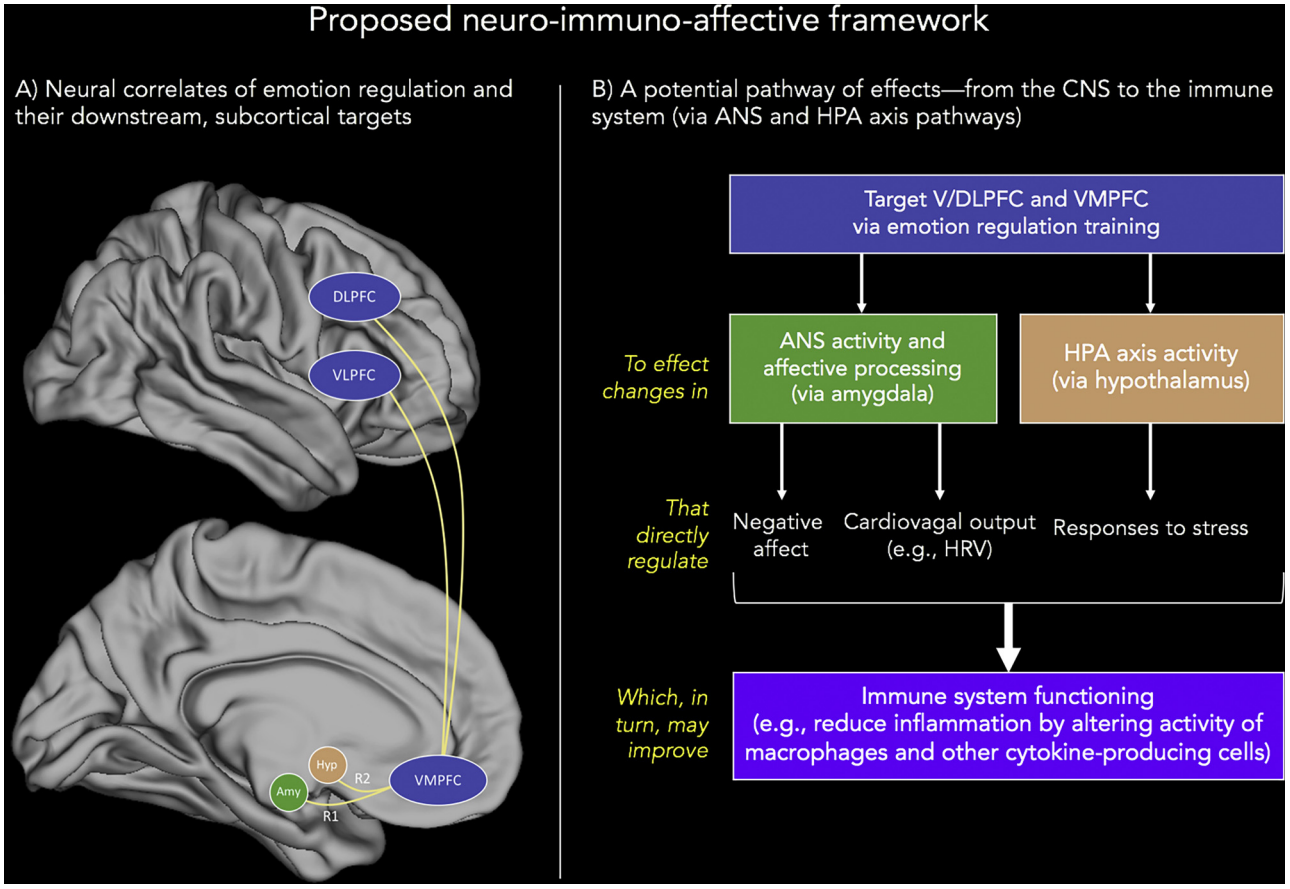

Fig. 1. Overview of the proposed neuro-immuno-affective framework: (A) PFC targets of emotion regulation (in blue), and routes of regulation—Route 1 (R1) to amygdala, in green, and Route 2 (R2) to hypothalamus, in orange/tan—localized on lateral and medial surfaces of a normalized (template) brain; (B) A potential pathway whereby targeting V/DLPFC and VMPFC (via emotion regulation training) would lead to a cascade of effects, first in the ANS and endocrine systems, and then in the immune system, including peripheral immune responses that may be characterized by lower inflammation (e.g., by reduced levels of circulating pro-inflammatory cytokines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

session (Zotev et al., 2013).

Given these studies' successes in administering emotion regulation skills training and observing concomitant changes in brain regions associated with emotion processing (e.g., amygdala) and regulation (e.g., VMPFC), our neuro-immuno-affective framework begins with multiple targets in PFC, including VLPFC, DLPFC, and VMPFC (see Fig. 1A), which represent modulation targets for emotion regulation skills training (e.g., increases in reappraisal-related activity in DLPFC). Next, drawing from what is already known about the functional neuroanatomy between cortical and subcortical systems, our framework consists of separate but equally important "routes" of regulation, which, when taken together, might confer benefits on mental health as well as the immune system via regulation of ANS/endocrine systems (see Fig. 1B).

The first route, represented by neuroanatomical connections between V/DLPFC, VMPFC, and amygdala (see R1 route depicted in Fig. 1A), would allow for down-regulation of negative appraisals that frequently present in affective disorders (e.g., negative and ruminative self-appraisals in depression; perceptions of threat and/or high arousal in anxiety). In support of this first regulatory route, the VMPFC has already been identified as a brain-based biomarker differentiating patients who go into remission following 12 weeks of treatment and patients who do not respond to treatment (McGrath et al., 2014), as well as a marker of treatment efficacy (Dichter et al., 2009; Ritchey et al., 2011). Another feature of this first regulatory route is that, assuming emotion regulation skills training results in greater recruitment of V/DLPFC and VMPFC, there may be attendant changes in ANS activation via the functional role that VMPFC–amygdala connections play in the cardiovagal control of heart rate and HRV (Sakaki et al., 2016)—via downstream signaling along efferent pathways of the vagus nerve (Thayer and Sternberg, 2010). Relatedly, difficulties in regulating emotion have been linked to decreased HRV (Williams et al., 2015), so by improving emotion regulation capacity there may be a cascade of effects—due to increased VMPFC activity more generally—observed in other systems (e.g., ANS) beyond the CNS.

The second regulatory route in our neuro-immuno-affective framework is from VMPFC to the hypothalamus (labeled as R2 in Fig. 1A). In this case, increased activity of V/DLPFC (and VMPFC) from improved emotion regulation processes may result in changes in molecular signaling in the HPA axis that help rein in a dysregulated (e.g., hypervigilant) stress response. In this way, previous impairments in HPA axis activity may be resolved, and given the bi-directional pathways that exist between the immune system and HPA axis (see Silverman and Sternberg, 2012 for a review), proinflammatory responses might be mitigated as well.

Taken together, we propose that these regulatory routes, originating in multiple regions of PFC with VMPFC as a potential regulatory "hub," may result not only in regulation of negative affect, but also support a healthier immune system (i.e., by reducing the inflammatory response)—via adaptive changes in ANS activity (e.g., increased HRV) and neuroendocrine processes (i.e., altered HPA axis activity). We would be remiss in not acknowledging that there are aspects of our framework—especially CNS/endocrine/immunological interactions and vagally-mediated control of immunological processes—that have been discussed elsewhere (see Chavan et al., 2017; Pavlov and Tracey, 2015). Indeed, studies by Muscatell and colleagues have provided

evidence for neuro-immuno relationships in particular, with one study showing that acute administration of pro-inflammatory endotoxin altered activity in brain regions associated with evaluative processing of social feedback (Muscatell et al., 2016). That said, one of the central features of our neuro-immuno-affective framework is targeting regions of PFC with emotion regulation skills training, which may act as a catalyst for downstream modulation across systems and confer benefits on health via improvements in affective experience, ANS activity, and immune system functioning.

4. Conclusions and implications for future work

We began this review by discussing the prevalence of affective disorders, namely depression and anxiety, and comorbidities that involve immune system dysfunction (i.e., hyperactive inflammatory response). Next, we argued that treatments of these disorders, including pharmacological treatments, are not as effective as they might be, and that more attention should be paid to neurobiological mechanisms that might account for both the inability to properly regulate affective responses and co-occurring immune dysfunction often seen in affective disorders.

To this end, we first highlighted work in clinical and affective neuroscience that has identified reliable neural correlates of adaptive (and less adaptive) emotion regulation strategies, including areas of dorsal and ventral PFC as well as medial PFC. Next, we drew upon other lines of work and showed that there is some neuroanatomical overlap in VMPFC, which plays an important modulatory role in other bodily systems (i.e., ANS/endocrine systems) that play a critical role in communicating with—and regulating—the immune system.

Based on this shared neurobiology, and multiple regulatory functions subserved by PFC (especially VMPFC), we have put forth a novel neuro-immuno-affective framework in which emotion regulation skills training, meant to target multiple PFC sub-regions, might positively improve mental and physical health via multiple regulatory routes (see Fig. 1A). Together, these routes positively impact brain function related to emotional experience (e.g., downregulation of amygdala activity) and well as activity in the ANS and endocrine system (i.e., HPA axis). Changes in these latter two systems may be especially important for improving immune system functioning—an important and sometimes overlooked treatment target in affective disorders.

A strength of this neuro-immuno-affective framework is that it is at once neurobiologically constrained by functional and anatomical features of sub-regions of PFC, while at the same time applicable to different patterns of affective dysfunction. That is, regardless of the downstream regulatory goal based on the disorder being treated (e.g., reducing anhedonia in depression, or extinguishing a fear response in the context of an anxiety disorder or phobia), V/DLPFC and VMPFC would serve as the primary brain-based targets of emotion regulation skills training. In the case of anhedonia in depression, the goal might be to down-regulate negative affect related to the self, and/or up-regulate positive appraisals more generally. Either way, DLPFC, and especially VLPFC, can be recruited to modulate value representations in VMPFC, which may modulate downstream activity in the amygdala reflecting negative appraisals (for down-regulation), and/or activity in the ventral striatum, a key subcortical region in the brain's reward circuitry that also plays a role in up-regulation of emotional experiences (Haber and Knutson, 2010; Wager et al., 2008). Indeed, lateral–medial PFC interactions have been observed in the appetitive domain that help support self-control related processes (Hare et al., 2009). Additionally, and as alluded to earlier, since the V/DLPFC–VMPFC and VMPFC–amygdala/hypothalamus pathways both have VMPFC in common, there may be functional "spillover" as a result of improving emotion regulation skills, such that emotion regulation may enhance VMPFC functioning not just in the context of regulating emotions, but more broadly. This might look like more effective regulation of the ANS (via the VMPFC–amygdala pathway) and/or the HPA axis (via the VMPFC–hypothalamus pathway).

As far as how future studies can implement our framework, we would suggest that researchers run randomized controlled trials in which patient and control/comparison groups are randomly assigned to emotion regulation skills training or an active control condition that is as engaging but relies on different brain systems (e.g., mindfulness-based treatments). The exact nature of the emotion regulation skills training can be properly tailored according to the emotion regulation deficits that are most problematic in the population under study. For example, in some cases, emotion regulation skills training may involve *increasing* the use of antecedent-focused strategies (i.e., cognitive reappraisal), *decreasing* use of response-focused strategies (i.e., expressive suppression) or a combination of both. Regarding the former, there are several cognitive reappraisal tactics that can be a part of emotion regulation skills training. One tactic is reinterpretation, which involves changing the meaning of an emotionally evocative event or stimulus so that appraisal or outcome is not as negative as it once seemed. Another tactic is psychological distancing, which involves appraising an emotional stimulus or event as a detached and impartial third-party observer (e.g., Kross and Ayduk, 2011; Verduyn et al., 2012).

Future emotion regulation research should compare the relative efficacy of reinterpretation and distancing on brain activity and accompanying longitudinal changes in ANS and HPA axis activity and immune functioning. A behavioral study comparing these two tactics in healthy adults suggests that distancing (versus reinterpretation) may be a more effective reappraisal tactic to reduce negative affect given its greater stimulus-independence (Denny and Ochsner, 2014), although it is not clear whether this pattern holds in clinical/patient samples. Another consideration for study design is dosage (e.g., one-shot cognitive reappraisal skills training versus multiple training/practice sessions). Lastly, as far as key covariates and dependent measures, future studies might consider subjective reports of positive/negative affect and patterns of reappraisal related brain activity (measured during an fMRI session) in emotion regulation regions, such as V/DLPFC and VMPFC, and their connectivity—with each other as well as with subcortical regions important for emotion processing (i.e., amygdala) and endocrine processes (i.e., hypothalamus in the HPA axis). These brain measures can then be examined as potential mediators between emotion regulation skills training condition(s) and relevant health outcomes, such as cardiovascular (e.g., HRV) and/or immunological (e.g., inflammation) measures. The rationale for this approach, especially as it relates to examining neural modulation of cardiovascular functioning, is warranted given the strong links between PFC activity and cardiovagal control (Thayer and Sternberg, 2010).

Despite the strengths and flexibility of our neuro-immuno-affective framework, there are some caveats we should mention. First, the framework has a directional hypothesis: target V/DLPFC and VMPFC with emotion regulation training in order to subsequently alter ANS and HPA axis activity and ultimately improve immune system function. However, in reality, the relationship may go in the other direction, with immune dysregulation representing the cause as well as the consequence of affective disorders. Indeed, some have recently proposed directly targeting the immune system to treat depression (Miller and Raison, 2016), while others have suggested that manipulating heart rate oscillations (e.g., by resonance breathing) may in turn change oscillatory activity in the brain and help improve emotion regulation (Mather and Thayer, 2018). Indeed, there is some evidence of immune system–to-brain pathways whereby inflammatory responses in the periphery modulate brain activity (e.g., Muscatell et al., 2016). Assuming such neuro-immuno relationships are at least somewhat reciprocal, with feed-forward and feed-backward connections, then targeting brain regions associated with emotion regulation, as we propose here, may nonetheless be efficacious and result in positive downstream effects (e.g., reduced stress and/or inflammatory responses). Also, it is worth mentioning that compared to immunotherapies, emotion regulation skills training is relatively inexpensive, easy to administer, and

scalable (e.g., can be delivered on recipients' own mobile devices).

In this review, we have attempted to integrate findings from clinical and affective neuroscience and psychoneuroimmunology to highlight the importance of neurobiological correlates of the experience and regulation of negative emotion, and the regulation of other physiological systems, including the ANS, endocrine, and immune systems. To conclude, our neuro-immuno-affective framework has implications for improving mental and physical health generally, and also for treating affective disorders in particular. With more collaborations and greater cross-talk between fields that pursue dynamic, multi-system interactions to understand processes that support and promote health (e.g., clinical/affective neuroscience and psychoneuroimmunology), we believe that our neuro-immuno-affective framework, and others like it, can be applied and tested more rigorously, with potential benefits spanning psychological and physical health.

Competing interests

The authors declare no competing interests.

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